

The Chiral Principles Contained in Structure–Sweetness Relations

Robert S. Shallenberger

New York State Agricultural Experiment Station,
Cornell University, Geneva, NY 14456, USA

ABSTRACT

Two chiral principles have been developed. When applied concertedly, they lead to a third principle. The latter affords a solution to the chiral anomaly presented by the fact that, whilst the sweet receptor site is chiral, and the D-amino acids are correspondingly sweet and the L-amino acids are not, both enantiomeric forms of the sugars taste sweet.

INTRODUCTION

In 1886, Piutti synthesized D-asparagine and noted with surprise that it tasted sweet, as the natural enantiomer, L-asparagine, is tasteless. In a note appended to Piutti's paper, Louis Pasteur remarked that, in view of these findings, the receptor site for sweet taste must therefore be 'dissymmetric' (chiral). Since that time it has been established (Solms *et al.*, 1965; Wiser *et al.*, 1977) that, with the exception of the first chiral member of the homologous series of amino acids (alanine), when a member of the D-series of amino acids tastes sweet the enantiomer is either tasteless (neutral) or bitter.

As the D-series of sugars usually taste sweet, it would seem to immediately follow, in recognition of the chiral nature of the receptor site, that the L-series of sugars must be tasteless or bitter. This seems to be a case of a deduction that is so 'obviously' correct, it is now difficult to

establish that it is, in fact, in error. However, L-allose and L-altrose (Austin & Humoller, 1934), and L-fructose (Wolfrom & Thompson, 1946) were reported earlier to taste sweet and, more recently, it was found (as anticipated) that an experienced taste panel could not distinguish between the sweet taste of enantiomeric pairs of arabinose, xylose, rhamnose, glucose, galactose and mannose (Shallenberger *et al.*, 1969). Finally, L-sucrose is also now known to taste sweet (Szarek & Jones, 1978). Therefore, a report (Boyd & Matsubara, 1962) confirming that first approximation implicit in the discovery that the sweet receptor site is chiral seems to have been solicitous.

However, a stereochemical problem (chiral anomaly) of rather high order is introduced by the finding that the L-series of sugars tastes sweet, as do the D-sugars, and yet the receptor is chiral. At the present time there is neither a symmetry principle nor a chiral principle alone that is capable of explaining this anomaly. Two fundamental chiral principles have recently been developed, however, and when they are applied concertedly, the result obtained affords a solution to the problem. The purpose of this paper is to demonstrate that solution.

FORMULATION OF CHIRAL PRINCIPLES

Definition of chirality

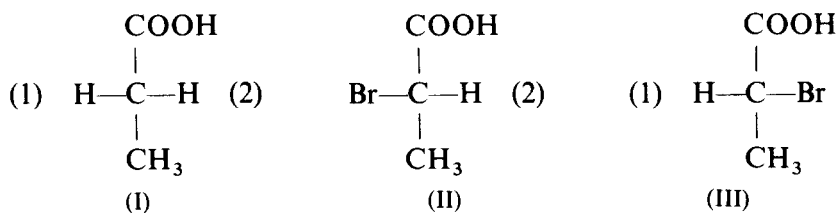
Chirality (handedness) is a topological attribute of a geometric structure leading to the potential for the occurrence of non-superposable mirror image structures, or *enantiomers*. In cases where the structure possesses several chiral features, e.g. sugars, it also leads to the potential for *diastereoisomerism*, or stereoisomers that are not enantiomers (Eliel, 1971).

Using symmetry expressions, it can be stated that a chiral structure does not possess any symmetry elements of the second kind (improper axes of symmetry) and it is therefore *asymmetric*. A *dissymmetric* structure retains a symmetry element, but is nevertheless chiral. Therefore, the treatment of degraded symmetry (dissymmetry) and the complete lack of symmetry (asymmetry) is encompassed by only one handedness specification. Both cases are examples of *chirality*. The alternative classification is then *achiral* (symmetrical).

Fundamental stereochemical concepts

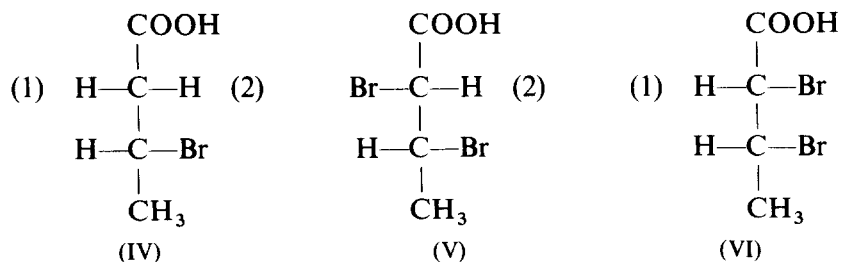
For subsequent thesis development several established and fundamental stereochemical concepts need to be introduced. Their nomenclature may seem difficult at first, but their conceptual significance is elegant and straightforward. The root concept is that chemical ligands and structural faces may display stereochemical non-equivalence, or *stereoheterotopicity* (Eliel, 1980). When one of two identical ligands of a chemical structure is substituted by a *different* group, chirality will result if those ligands are stereochemically *heterotopic*, with respect to the remainder of the molecule, and not *homotopic*. For example (Eliel, 1980)—the two hydrogen atoms of methylene chloride, CH_2Cl_2 , are homotopic as the replacement of one of them by another group, such as bromine, leads to CHBrCl_2 , and the molecule has no isomers.

The hydrogen atoms in propionic acid (I), however, are *enantiotopic*. Replacement of H(1) alone by bromine (II) forms one of a pair of possible bromopropionic acid enantiomers, and replacement of H(2) alone by bromine leads to the other (III).



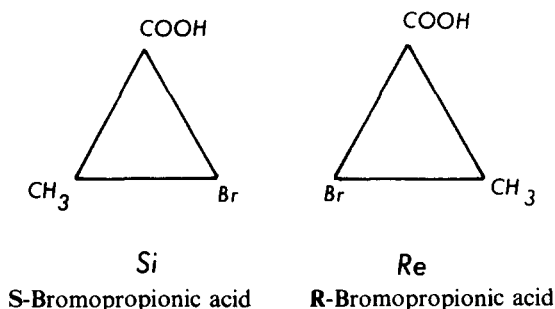
In compounds such as 3-bromobutanoic acid (IV), the hydrogen atoms H(1) and H(2) are *diastereotopic* since replacement of H(1) alone by bromine leads to *threo*-2,3-dibromobutanoic acid (V) and replacement of H(2) alone leads to *erythro*-2,3-dibromobutanoic acid (VI). The latter two compounds are *diastereoisomers*.

The principles of heterotopicity can be employed in two ways. The



first is abstract and is the anticipation of the chirality that will result when a ligand or face is substituted by a different group. Thus, H(1) in propionic acid is pro-**S** and H(2) is pro-**R** as compounds (II) and (III) are **S**- and **R**-bromopropionic acid (Cahn *et al.*, 1966), respectively. Those hydrogen atoms are therefore *prochiral* (Hanson, 1966).

The second use of the heterotopicity concept is for direct description of existing chiral features, for comparative purposes. The plane formed by Br, COOH, CH₃ on **R**-bromopropionic acid is configurationally enantiotopic to the plane formed by the same groups on **S**-bromopropionic acid.



When dealing with the relationship between substituents on a planar surface of a three-dimensional structure, a problem of specifying their chirality arises, as the plane has two sides, but the front and rear faces can be differentiated (Eliel, 1980) in a manner similar to that used to distinguish three-dimensional enantiomers (Cahn *et al.*, 1966). The tripartite front face of **S**-bromopropionic acid, with the priority sequence CH₃ → Br → COOH, is counterclockwise, and labeled **Si**. The sequence in the enantiomer is clockwise and labeled **Re** (both the **R** and **Re** symbols stand for *rectus*, **S** and **Si** for *sinister*). The back face for each plane then has the configuration of the enantiomer.

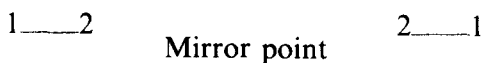
The use of the heterotopicity idea as applied to planar faces of substances is of primary importance in this discussion. As applied to substances, such faces are necessarily one-sided.

Formulation of chiral principles

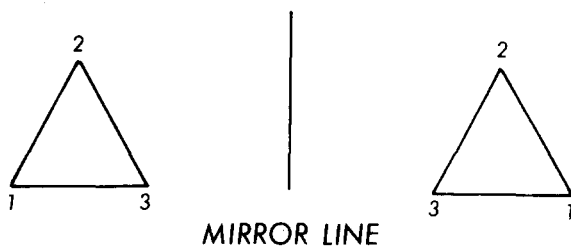
The development of chiral principles now presented is an extrapolation of the conceptual approach to that subject devised by Prelog (1976) in order to emphasize the significance of chirality in chemistry. The first two principles (numbering and puckering operations) have recently been

employed (Shallenberger *et al.*, 1981; Shallenberger, 1982) to algebraically calculate and unambiguously specify the multiple chirality displayed by sugar ring structures. At a more fundamental level it will be seen that those two principles, when applied concertedly, are capable of transgression between spatial continuums.

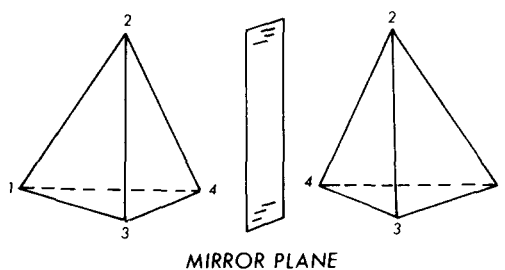
Principle one. Differential labeling of a regular (symmetrical) geometric structure generates a chiral structure. Therefore, differential labeling (numbering, lettering, coloring) of a regular structure is a chiral operation. In one dimension (1-space) it is the labeled line, and its enantiomer, formulated by mirror-point reflection, is not superposable upon it.



In two dimensions (2-space) the simplest chiral structure is the differentially labeled regular (equilateral) triangle. Its enantiomer is formulated by mirror-line reflection, as shown below, and the two structures are *configurationally enantiotopic*.



In three dimensions (3-space) the simplest chiral structure is the differentially labeled regular tetrahedron. Its enantiomer is formulated by mirror-plane reflection and the two structures are again configurationally enantiotopic.



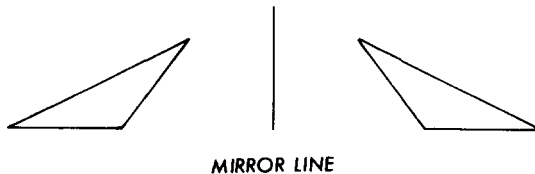
The exercise in 3-space is immediately recognizable as the basis for the theory of the asymmetric tetrahedral carbon atom.

In this latter context, two *attributes* of chirality can now be developed. The first is that traditional configurational isomerism is a mirror-point differential label transposition (*in situ* inversion through a mirror point) in 1-space. All that is required in order to transpose a labeled regular geometric structure in a higher spatial continuum to its enantiomer is to execute, as a chiral operation, a 1-space differential label transposition. Thus, the two labeled lines in one space are configurational isomers, and one is readily converted to the other by inversion through a central (bisecting) mirror point.

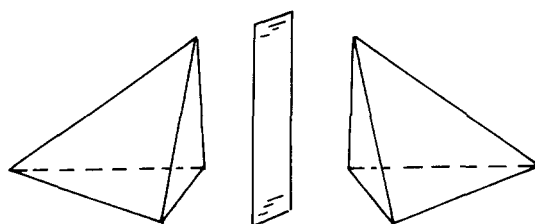
In 2-space the labeled regular triangles are transformed by the inversion of only two (any two) labels on either one of them. The attribute also holds for the differentially labeled regular tetrahedrons, as students of the asymmetric carbon atom are again well aware. Therefore, configurational isomerism is essentially a 1-space concept that can neatly be executed in higher spatial continuums. As a consequence, when a geometrical structure is regular, but differentially labeled, *the definition of configurational isomerism and enantiomerism converge*.

The second attribute is that the chirality that prevails in one spatial continuum is lost in the next highest continuum. In 1-space the chirality displayed by the labeled line is lost (carried back into itself) in 2-space because rotation, as a symmetry operation, is possible, leading to superposability. The chirality displayed by the labeled regular triangle in 2-space is lost, through rotation, in 3-space. Finally, the chirality displayed by the differentially labeled tetrahedron is carried back into itself by rotations in the space-time continuum. Chirality of a higher order will still prevail in the latter continuum, however. In this sense, chirality, as well as symmetry, is a universal theme.

Principle two. Skewing a regular geometrical structure forms a chiral structure. Therefore, distortion (skewing, puckering, warping) of a geometrical structure is a chiral operation. As it is not possible in 1-space, the simplest skewed structure is the scalene triangle in 2-space. Reflection in a mirror line forms the non-superposable mirror-line enantiomer, and the two structures shown below are *conformationally enantiotopic*.



The 3-space sequel to skewing is puckering, but the first term applies equally to higher continuums. In 3-space, the simplest distorted structure is the irregular tetrahedron, with an element of chirality of higher order. Such a structure is not superposable upon its mirror-plane structure, and the forms shown below are *conformationally enantiotopic*.



MIRROR PLANE

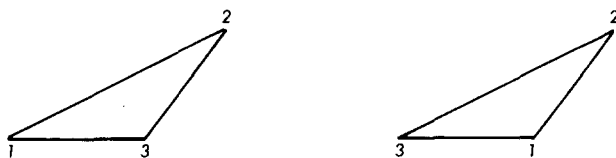
The aforementioned chiral attributes that were applied to principle one apply to principle two, also. The traditional conceptualization of conformational isomerism is, at the first spatial continuum where it is encountered, a distortion operation. All that is required to transform a skewed chiral structure to its enantiomer in any continuum (2-space or higher) is to skew it in the opposite direction, to the same extent. Other conformational isomers arise by only partial skewing in the opposite direction. Skewing, then, is essentially a 2-space chiral operation that may be executed in higher spatial continuums. Moreover, when an irregular structure is unlabeled, *the definition of enantiomerism and conformational isomerism may converge*. Conformational (shape) chirality, as defined in a given dimension, is also carried back into itself in the next highest dimension, but distortion chirality will exist in the higher dimension, and is of higher order.

The combination of principles one and two now leads to principle three, which has three *components*.

Principal three. The differential labeling of a skewed structure in a given spatial continuum leads to:

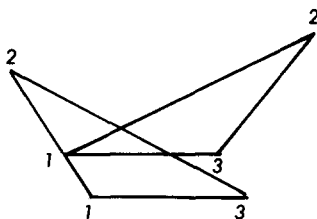
(a) *Configurational isomers in a given spatial continuum that become conformational isomers only in the next highest continuum.*

The structures shown below are configurational isomers in 2-space because two labels have been transposed on one item. In other words, the two structures are configurationally diastereotopic.



Configurational isomers in 2-space.

In 3-space, the labels can be ordered in the same direction, e.g. clockwise, but, because the shapes are not now congruous, and are, in fact, the 2-space enantiomeric conformations, the structures cannot be superposed.

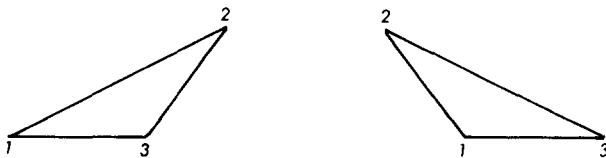


Conformational isomers in 3-space.

In formal stereochemical syntax, principle 3(a) states that, for an irregular structure, configurationally diastereotopic isomers in one spatial continuum are conformationally diastereotopic in the next highest continuum. The above structures in 2-space were therefore conformationally prodiastereoisomeric.

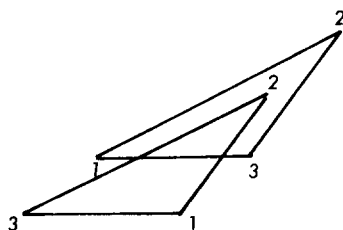
Each of the structures shown in 2-space has two additional configurational and two additional conformational diastereoisomers. They are not shown here, but several of them appear in the ensuing discussion.

(b) *Conformational isomers in a given spatial continuum that become configurational isomers in the next highest continuum.* Principle 3(b) is therefore the inverse of 3(a). The two labeled structures shown below are conformational isomers in 2-space (the labels are ordered in the same direction).



Conformational isomers in 2-space.

The above structures are, however, configurational isomers in 3-space that possess the same conformation. As shown below, while the conformations are superposable in 3-space, their configurations are not.



Configurational isomers in 3-space.

Thus, labeled *conformationally diastereotopic* structures in a given spatial continuum are *configurationally diastereotopic* in the next spatial continuum. The conformational isomerism of 2-space is lost in 3-space, but in 2-space the labeled conformational isomers are pro-configurationally diastereotopic.

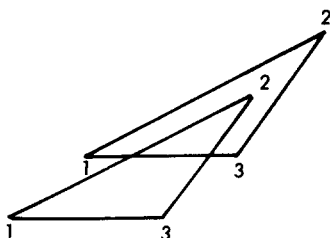
While principle 3(b) is the inverse of 3(a), their joint application leads to a highly significant result, which is principle 3(c).

(c) *Enantiomers in a given spatial continuum, which are both configurational and conformational (conversional) enantiomers, then become congruent in the next highest spatial continuum.* The two structures shown below are 2-space enantiomers in both the configurational and conformational sense.



Enantiomers in 2-space.

One of the structures above is formed from the other by the twofold operation of inverting the configuration of two of the labels about a mirror-point, and everting the conformation about a mirror line. The execution of the twofold operation (conversion) carries the enantiomerism displayed by the structures back into itself in 3-space.



Superposable structures in 3-space.

Thus, configurationally and conformationally enantiomeric structures in one spatial continuum are enantiotopic in that spatial continuum, but are homotopic in the next highest continuum. The conversional enantiomers in 2-space were therefore prostereohomotopic to 3-space.

THE CHIRAL NATURE OF SWEETNESS

The glychophore (Greek *glyks*, sweet; *phoros*, to carry) contained in the multitude of sweet-tasting compounds (sugars, amino acids, saccharin, etc.) is made up of an AH and a B unit prerequisite for the initial chemistry of the sweet-taste sensation (Shallenberger & Acree, 1967). AH is a proton donating group and B is a proton accepting group, each in the sense of hydrogen bonding theory. Accompanying AH, B is a lipophilic-hydrophobic parameter (Deutsch & Hansch, 1966; Shallenberger & Lindley, 1977), specified as ' γ '. The γ component need not be present as a specific functional group, as does AH, B, but when it is present as a functional group, it seems to be associated with the amplification of sweetness (Kier, 1972; van der Heijden *et al.*, 1978) or the activation of AH, B (Shallenberger & Lindley, 1977). In the latter two capacities, its position in space with respect to AH and B seems to be directional, rather than positional, but, most importantly, the geometry among the three groups describes a *planar scalene triangle*, thereby rendering the planar structure *doubly chiral*. The glychophore structure shown below is that for the D-amino acids (Kier, 1972) and the D- and L-hexoses (Shallenberger & Lindley, 1977). The distance parameters are A, B 2.6 Å, B, γ 5.5 Å, and A, γ 3.5 Å. The AH proton, B orbital distance is about 3 Å.

the initial chemistry of sweet taste that affords an answer to the problem created by the fact that while the D- and L-amino acids have different abilities to elicit sweet taste, the enantiomeric sugars are equally sweet. The answer is derived by applying the aforementioned chiral principles and stereochemical concepts.

RESOLUTION OF THE CHIRAL ANOMALY

Both D-amino acids and the D- and L-sugars contain the planar scalene and doubly chiral tripartite glycophore. For compounds without a γ functional group, γ is merely an element of lipophilicity, especially in small sweet-tasting molecules such as ethylene glycol and chloroform. These compounds do not possess stereoisomers, and their glycophore is therefore homotopic.

The D- and L-amino acids

The initial explanation (Shallenberger *et al.*, 1969) for the varying sweetness of the enantiomeric amino acids was to position a spatial barrier behind the receptor B, AH unit so that the 2-space geometry of the non-sweet isomer simply could not be placed over the receptor site. An element of truth in this deduction yet remains, as γ may be located on a spatial barrier, and the stereogeometry of AH, B and γ would yet be retained.

However, in view of the chiral principles that were formulated, a more defensible answer can now be proposed. Two of the reactive sites and, more specifically, those two essential for the sweetness attribute (AH, B) are attached to a single chiral center for amino acids while γ lies elsewhere in the molecule (for the amino acids, AH is NH_2 and B is $\text{C}=\text{O}$). The tripartite glycophore of the D-amino acid must be configurationally diastereotopic to the receptor only, and therefore superposable upon it in such a way that the concerted intermolecular H-bonding phenomenon occurs.

To convert a D-amino acid to an L-amino acid requires that NH_2 and COOH be transposed about the single chiral center. The effect on the glycophore is to merely transpose AH and B. Hence, for the 2-space glycophore structure for the enantiomeric amino acids, the structures are configurationally diastereotopic and conformationally homotopic. In 3-space, however, and in accordance with principle 3(a), the planar and one-

sided enantiomeric glycochore structures are conformationally diastereotopic and configurationally homotopic. Therefore, as shown in Fig. 2, D-asparagine can be superposed upon the receptor site, but the enantiomer cannot because it is conformationally and configurationally diastereotopic with the receptor, and therefore not superposable upon it in such a way as to permit a tripartite interaction.

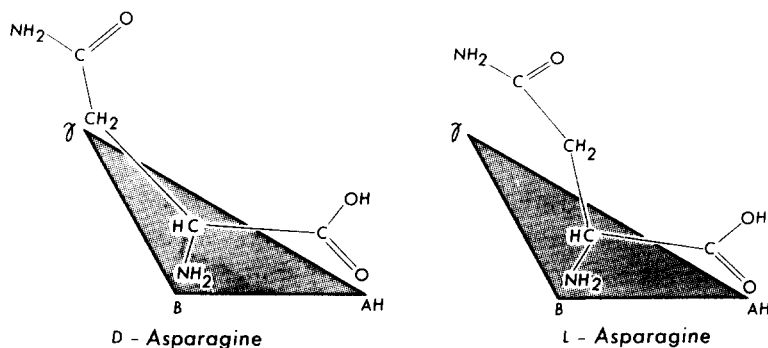


Fig. 2. Superpositioning of the tripartite glycochore of D-asparagine over the receptor site versus the inability to position the conformationally diastereotopic L-asparagine glycochore.

Parenthetically, principle 3(a), as applied to the amino acids, seems to be the conformational sequel to the concept of (configurational) prochirality (Hanson, 1966). It should also be noted that, while the position of γ for the glycochore is appropriate for the sugars, as will be seen subsequently, and also the small molecules that are homotopic, it could be farther removed for the amino acids than depicted. While L-alanine is sweet, D-alanine is sweeter, however (Berg, 1953). Nevertheless, the principles being developed still hold.

The D- and L-sugars

In spite of the spatial barrier that was invoked in order to explain the lack of sweetness for L-amino acids, it was recognized that any vicinal pair of sugar OH groups, acting as AH, B, could be superposed upon an AH, B receptor site. In the case of D-sugars by direct superpositioning, and in the case of L-sugars, merely by inverting the molecule. It was for this reason that sweetness similarity for D- versus L-sugars was the only conclusion possible for the original (Shallenberger & Acree, 1967) AH, B thesis, and which subsequently proved to be the case (Shallenberger *et al.*, 1969).

above the molecule. Obviously, the two sugars are 3-space enantiotopic structures and are not superposable in 3-space. It can also be seen that the glycochophores are enantiotopic, but the enantiotopism is planar enantiotopism on the face of the three-dimensional structures. In other words, the fructose glycochophores are 2-space enantiotopic. In 3-space they are superposable by invoking a simple rotational operation, in accordance with principle 3(c). Therefore, both the D- and L-glycochophores of fructose are merely configurationally diastereotopic with the receptor site, the requirement for interaction with it.

The reason why principle 3(c) applies to the sugars and not to the amino acids is due to the fact that the former are doubly chiral, with AH, B situated on separate carbon atoms. The latter are singly chiral with AH, B located upon a single chiral center. The glycochophores of the enantiomers of the former are 2-space enantiotopic, and 3-space homotopic (principle 3(c)). Those of the latter are 2-space configurationally diastereotopic and 3-space conformationally diastereotopic (principles 3(a) and 3(b)).

Just how the double chirality of the sugars leads to planar 2-space enantiotopic glycochophores for D- and L-sugars is shown in Fig. 3. β -D-Glucopyranose is converted, in the Figure to β -L-glucopyranose by executing two chiral operations. The Mills' (1955) structure for glucopyranose is shown along with the conformational structures so that the fate of the glycochophore may be followed during the enantiomeric conversion. The Mills' structure depicts the conformational structure from directly 'above' the molecule so that the puckering mode of the isometric model is 'extinguished', but the direction of the ring carbon—carbon bonds is then indicated by darts and hatched lines. In the Mills' structure, only carbon atom substituents in an equatorial disposition can be shown, but the tripartite geometry of the D-glycochophore is readily apparent. As a final comment with reference to Fig. 3, replacing the central structures with a mirror placed 'below' the β -D-glucopyranose structures will give the reflected final structures for β -L-glucopyranose.

To convert β -D-glucopyranose (C1) to the enantiomer first requires that the configuration about each chiral center be inverted. In executing this operation, all equatorial substituents become axial, and vice versa. The tripartite geometry of the glycochophore is lost with this operation. In performing the second operation (eversion of the conformation) the tripartite glycochophore geometry reappears as all equatorial and axial substituents are transposed. The geometry reappears even though AH, B and γ are located on carbon atoms that have the opposite configuration.

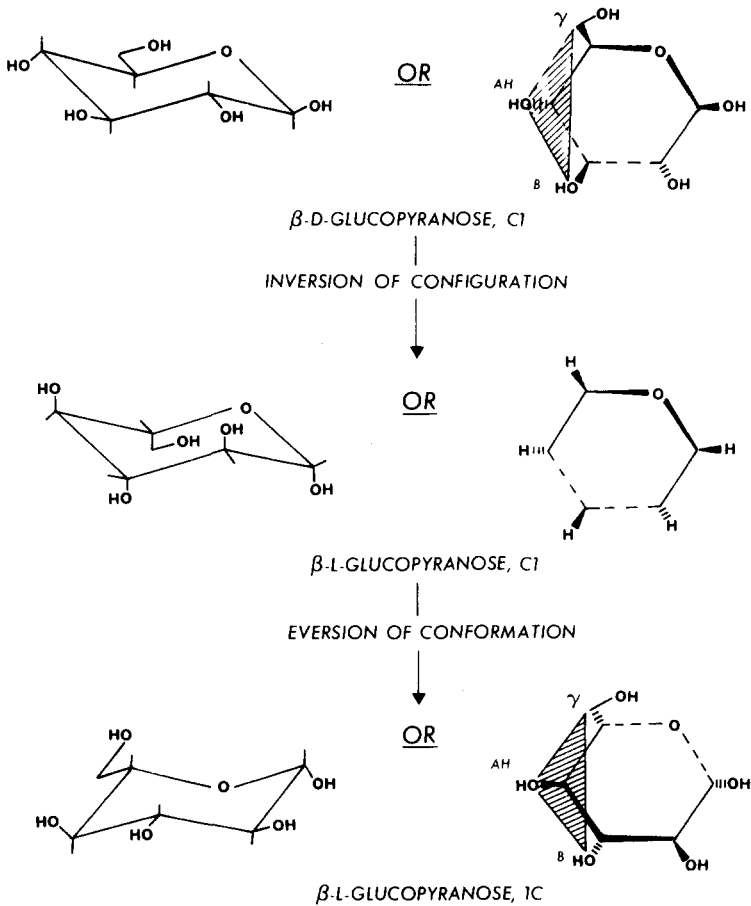
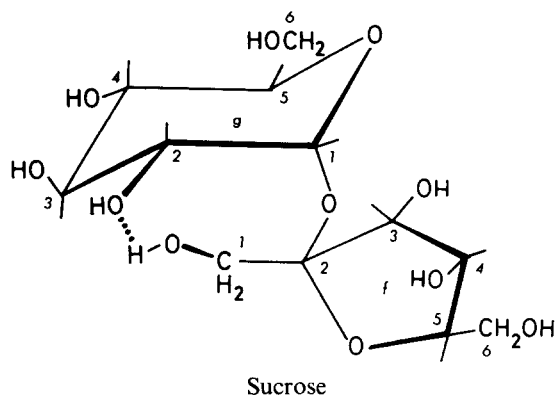


Fig. 3. The fate of β -D-glucopyranose glycophore upon conversion of β -D-glucopyranose C1 to β -L-glucopyranose IC.

What has actually happened is that the 'back face' of the D-glucopyranose tripartite glycophore has been formed by the two operations. The front face of the glycophore in β -D-glucopyranose, which is on the 'bottom' of the molecule, is Si ($\gamma \rightarrow B \rightarrow AH$). Its back face is therefore Re. In 3-space, however, it is congruent to the D-glycophore. Thus, the tripartite geometry of the sweet glycophore for a D-sugar versus an L-sugar is carried back into itself in 3-space. The sequence of inversion and eversion in Fig. 3 can be reversed, but the result will be the same.

The sweetness of both the D- and L-forms of sucrose is qualitatively

indistinguishable (Dinda *et al.*, 1982). While the α -D-glucopyranosyl moiety of sucrose is a possible glycochore for sucrose (Shallenberger, 1979), the sweetness-structure attributes of the compound present problems. In the first place, on an equimolar basis, sucrose is nearly three times as sweet as glucose. Therefore, the primary glycochore for sucrose is not likely to be 'just' the glucose residue. Furthermore, the β -D-fructofuranose moiety of sucrose can only participate in glycochore formation through some structural feature other than its furanoid form, as free β -D-fructofuranose is devoid of sweet taste (Shallenberger, 1978). Finally, if the hexose sugars can be said to be doubly chiral (due to the chiral centers for the carbon atoms and the chiral axis for the rings), then sucrose can be said to be triply chiral, and the additional feature is the helical pattern of chirality presented by the glycosidic linkage. The structure of sucrose in water solution has now been established (Boch & Lemieux, 1982), and is shown below.



An heretofore unknown feature of the structure is that O—1^f is intramolecularly hydrogen bonded to O—2^g. With the conformation of the glycosidic linkage so established, it is found that, in addition to the glucose moiety, sucrose has two additional AH, B, γ glycochores. They are:

	1	2
AH	OH—3 ^g	OH—2 ^g
B	O—4 ^g	O—3 ^g
γ	C—1 ^f	C—1 ^f

The OH—2^g unit had previously been proposed as being AH to explain

the sweetness of tetrachloro episucrose (Hough & Phadnis, 1976), and, more recently as AH for sucrose itself (Boch & Lemieux, 1982). The interesting result is that the glycochore components, which had previously been assigned to *exo*- and *endo* components of hexose ring structures, are now located on the different sugar residues of sucrose. Even so, the transposition of the D- to the L-sugar apparently carries the sweet-tasting glycochores back into themselves because of the multiple chirality that is displayed by the sucrose structure.

REFERENCES

- Austin, W. C. & Humoller, F. L. (1934). The preparation of two new aldohexoses, L-allose, and L-altrose, from L-ribose by the cynohydrin reaction. *J. Am. Chem. Soc.*, **56**, 1153.
- Bentley, R. (1978). Ogsten and the development of prochirality theory. *Nature*, **276**, 673-6.
- Berg, C. P. (1953). Physiology of D-amino acids. *Physiol. Rev.*, **33**, 145-89.
- Birch, G. G., Lee, C. K. & Rolfe, E. J. (1970). Organoleptic effect in sugar structures. *J. Sci. Fd. Agric.*, **21**, 650-3.
- Boch, K. & Lemieux, R. U. (1982). The conformational properties of sucrose in aqueous solution: Intramolecular hydrogen-bonding. *Carbohyd. Res.*, **100**, 63-74.
- Boyd, W. C. & Matsubara, S. (1962). Different tastes of enantiomorphic hexoses. *Science*, **137**, 669.
- Cahn, R. S., Ingold, C. K. & Prelog, V. (1966). Specification of molecular chirality. *Angew. Chem. Int. Ed. (Engl.)*, **5**, 385-415.
- Deutsch, E. W. & Hansch, E. (1966). Dependence of relative sweetness on hydrophobic bonding. *Nature*, **211**, 75.
- Dinda, R. K., Beck, I. T., Szarek, W. A., Hay, G. W., Ison, E. R. & Vyas, D. (1982). Evidence that L-sucrose is resistant to hydrolysis by jejunal brush border enzymes. *Can. J. Physiol. and Pharm.*, **60**, 652-4.
- Eliel, E. L. (1971). Recent advances in stereochemical nomenclature. *J. Chem. Educ.*, **48**, 163-7.
- Eliel, E. L. (1980). Stereochemical non-equivalence of ligands and faces (heterotopicity). *J. Chem. Educ.*, **57**, 52-5.
- Hanson, K. R. (1966). Applications of the sequence rule. *J. Am. Chem. Soc.*, **88**, 2731-42.
- Hough, L. & Phadnis, S. P. (1976). Enhancement in the sweetness of sucrose. *Nature*, **263**, 800.
- Kier, L. B. (1972). A molecular theory of sweet taste. *J. Pharm. Sci.* **61**, 1394-7.
- Lemieux, R. U. & Brewer, J. T. (1973). Conformational preferences for solvated hydroxymethyl groups in hexopyranose structures. In: *Carbohydrates in solution*. (Isbell, H. S. (Ed.)). Adv. Chem. Series 117. Amer. Chem. Soc., Washington, DC.

- Lindley, M. G. & Birch, G. G. (1975). Structural functions of taste in the sugar series. *J. Sci. Fd. Agric.*, **26**, 117-24.
- Mills, J. A. (1955). The stereochemistry of cyclic derivatives of carbohydrates. *Adv. Carbohyd. Chem.*, **10**, 1-53.
- Piutti, M. C. R. (1886). Asparagine. *C. R. Acad. Sci. Paris*, **103**, 134-7.
- Prelog, V. (1976). Chirality in chemistry. *Science*, **193**, 17-24.
- Shallenberger, R. S. (1978). Intrinsic chemistry of fructose. *Pure and Appld. Chem.*, **50**, 1409-20.
- Shallenberger, R. S. (1979). Molecular chemistry of sweetness. *Zuckerind*, **104**, 121-4.
- Shallenberger, R. S. (1982). *Advanced sugar chemistry*, Avi Pub. Co., Westport, CT.
- Shallenberger, R. S. & Acree, T. E. (1967). Molecular theory of sweet taste. *Nature*, **216**, 480-2.
- Shallenberger, R. S., Acree, T. E. & Lee, C. Y. (1969). Sweet taste of D- and L-sugars and amino acids and the steric nature of their chemo-receptor site. *Nature*, **221**, 555-6.
- Shallenberger, R. S. & Lindley, M. G. (1977). A lipophilic-hydrophobic attribute and component in the stereochemistry of sweetness. *Fd. Chem.*, **2**, 145-53.
- Shallenberger, R. S., Wrolstad, R. E. & Kerschner, L. E. (1981). Calculation and specification of the multiple chirality displayed by sugar pyranoid ring structures. *J. Chem. Educ.*, **58**, 599-601.
- Solms, J., Vuataz, L. & Egli, R. H. (1965). The taste of L- and D-amino acids. *Experientia*, **21**, 692.
- Szarek, W. A. & Jones, J. K. N. (1978). L-sucrose and process for producing same. Belgian Pat. 866171.
- van der Heijden, A., Brussel, L. P. B. & Peer, H. G. (1978). Chemoreception of dipeptide esters: A third binding site. *Fd. Chem.*, **3**, 207-11.
- Wiser, H., Jugel, H. & Belitz, H. D. (1977). Relationships between structure and sweet taste of amino acids. *Z. Lebensm. Untersuchs-Forsch.*, **164**, 277-82.
- Wolfrom, M. L. & Thompson, A. (1946). L-Fructose. *J. Am. Chem. Soc.*, **68**, 791-3.